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# Detection of haplotypes responsible for prenatal death in cattle

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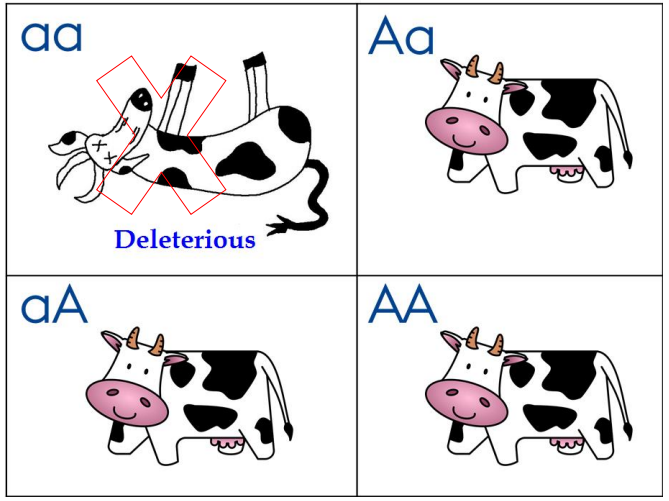
# Recessive deleterious alleles

## High frequency

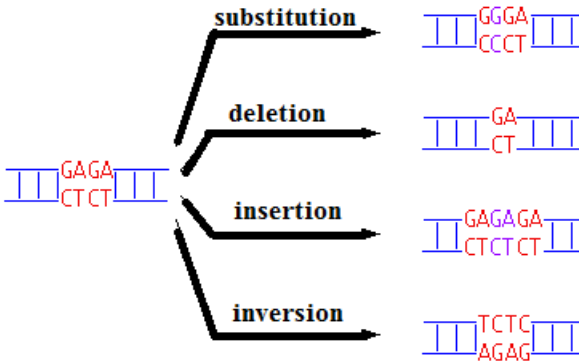
- by chance ~ genetic drift
- due to selection ~ linked to something valuable




**Use of a limited number of elite sires ~ increase the risk of deleterious allelic variants being homozygous**

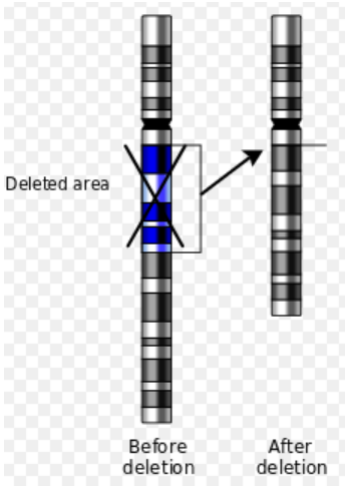
# Type of variants

- **Point mutations**




http://carolguze.com/text/442-2-mutations.shtml

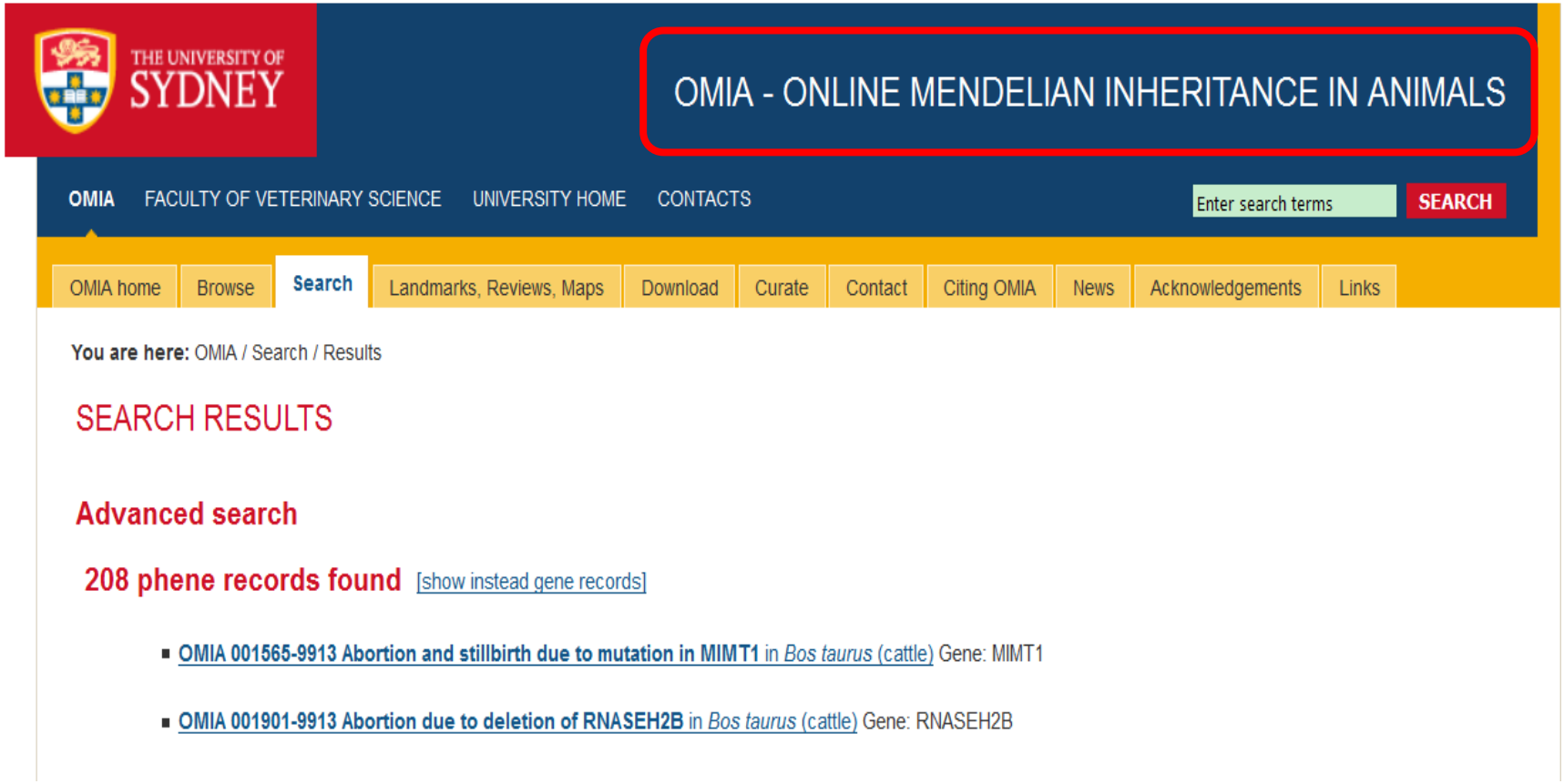
- **Chromosomal deletions**




National Human Genome Research (USA)

- **Putative haplotypes identified through loss of homozygosity**

# Known recessive deleterious alleles

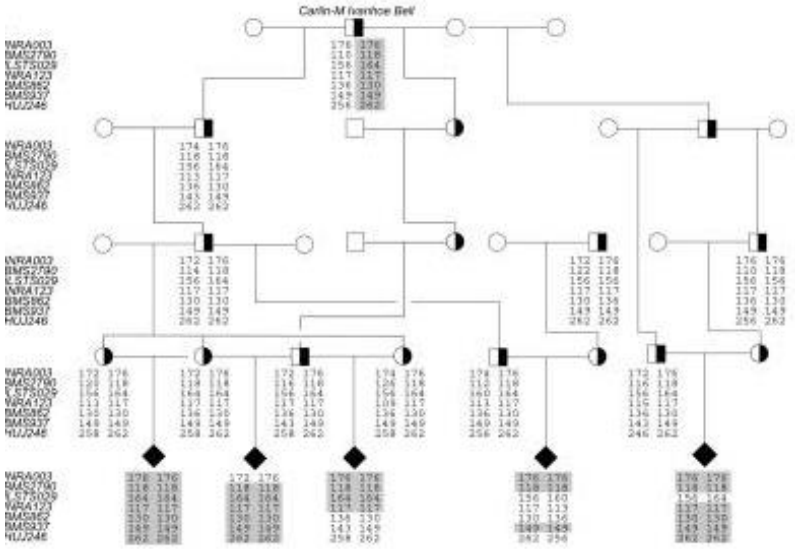


# Conventional detection approach

**From phenotype to genotype**

- Tracing Pedigree
- Finding chromosome segments where defect calves are homozygotes for an allele in common ancestor
- Live-born calves are never homozygotes

Thomsen et al., 2006



Complex vertebral malformation (CVM)

# ‘New’ detection approach

**From genotype to phenotype**

- Using genotype data (VanRaden et al. 2011)
- Haplotypes common in population, but no homozygous among live animals
- Requires genotypes only from live animals, but not from affected embryos/calves

# Aim and objectives

**To avoid loss due to recessive lethal carriers in cattle industry**

**Objectives:**

- To detect the recessive lethal haplotypes in three cattle breeds
- To identify casual genetic factors underlying these haplotypes

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# Data

## Bovine 50k

- HOL 26,312
- RDC 19,309
- JER 4,291

## Full sequence

- HOL 57
- RDC 56
- JER 27

# Method

## From genotype to phenotype

- Phased, 47k SNPs
- Window: 25 markers
- Compared Obs. homozygotes vs. Exp. homozygotes
- Exp. =(genotyped individuals No.)*$H^2$ ,

  H is haplotype frequency (assume random mating)
- Chi-square test

# Method

- **Whole genome sequence variants**

  Sequence depth

  Concordance among carrier and non-carrier

- **Phenotype: Reproductive failure**

  Carrier-sire by carrier-dam mating vs. other matings

# Detected haplotypes for HOL

| Chr. | Freq. | Obs. | Exp. | P-value | Pos.(Mbp) | Reported |
|---|---|---|---|---|---|---|
| 4 | 0.028 | 2 | 15 | 7.89E-04 | 11.5-13.0 | New |
| 6 | 0.069 | 87 | 124 | 8.92E-04 | 53.9-55.0 | HH7 |
| 7 | 0.086 | 141 | 193 | 1.82E-04 | 78.8-80.0 | HH8 |
| 8 | 0.025 | 0 | 17 | 3.74E-05 | 95.9-97.2 | HH3 |
| 9 | 0.028 | 2 | 20 | 5.70E-05 | 90.3-91.5 | HH5 |
| 11 | 0.105 | 183 | 291 | 2.43E-10 | 23.4-24.3 | 11-926 |
| 15 | 0.040 | 21 | 43 | 7.94E-04 | 77.2-78.7 | HH12 |
| 19 | 0.020 | 0 | 11 | 9.11E-04 | 8.28-9.41 | 19-151 |
| 21 | 0.029 | 0 | 22 | 2.73E-06 | 20.4-21.4 | BY |
| 26 | 0.025 | 1 | 16 | 1.77E-04 | 3.83-5.47 | New |

**CVM, BLAD... not detected**

# Detected haplotypes for RDC

| Chr. | Freq. | Obs. | Exp. | P-value | Reported |
|---|---|---|---|---|---|
| 1 | 0.028 | 1 | 15 | 3.01E-04 | New |
| 1 | 0.026 | 0 | 13 | 3.11E-04 | New |
| 1 | 0.025 | 0 | 12 | 5.32E-04 | New |
| 4 | 0.027 | 0 | 14 | 1.83E-04 | New |
| 7 | 0.027 | 1 | 14 | 5.12E-04 | New |
| 12 | 0.051 | 0 | 50 | 1.54E-12 | LH12(660kb) |
| 17 | 0.024 | 0 | 11 | 9.11E-04 | PIRM |
| 21 | 0.027 | 1 | 14 | 5.12E-04 | New |
| 21 | 0.027 | 1 | 14 | 5.12E-04 | New |
| 23 | 0.029 | 0 | 16 | 6.33E-05 | New |

# Detected haplotypes for JER

| Chr. | Freq. | Obs. | Exp. | P-value | Reported |
|---|---|---|---|---|---|
| 1 | 0.053 | 0 | 12 | 5.32E-04 | New |
| 3 | 0.061 | 1 | 16 | 1.77E-04 | New |
| 5 | 0.067 | 1 | 19 | 3.64E-05 | New |
| 8 | 0.058 | 1 | 14 | 5.12E-04 | New |
| 20 | 0.061 | 1 | 16 | 1.77E-04 | New |
| 22 | 0.055 | 1 | 13 | 8.74E-04 | New |

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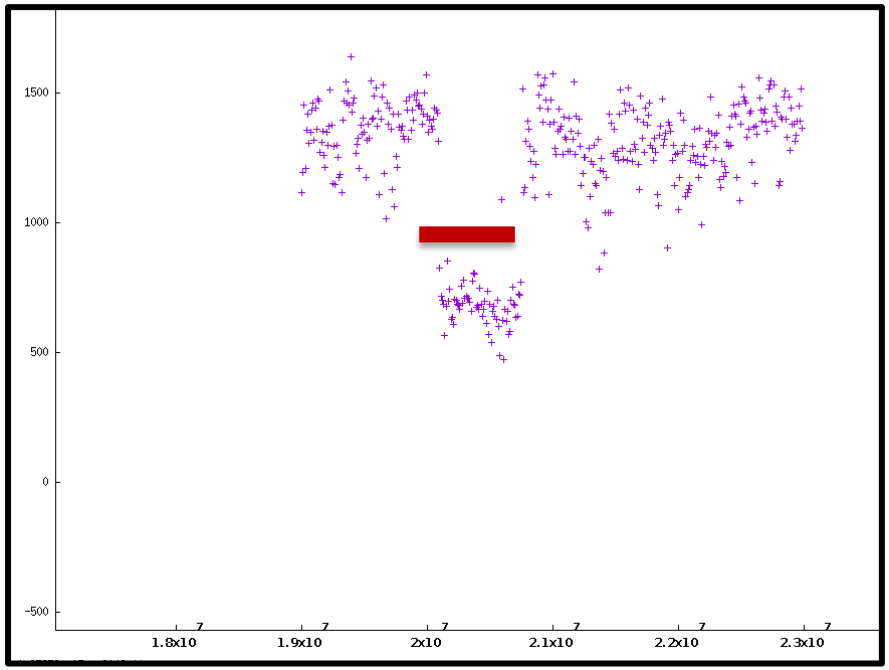
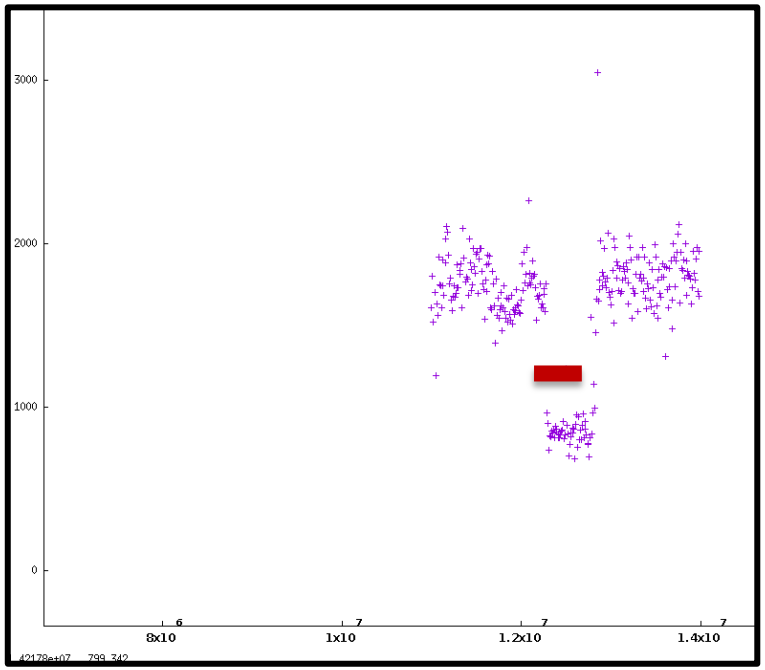
# Large chomosomal deletions

## Sequence depth




660kb deletion, Kadri et al, 2014

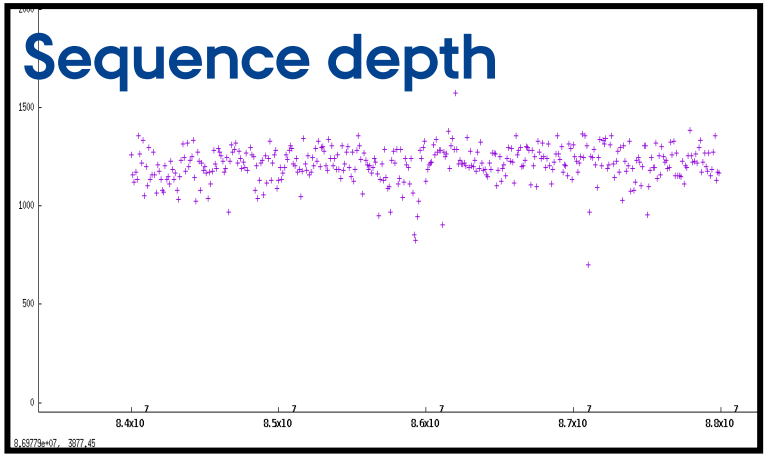


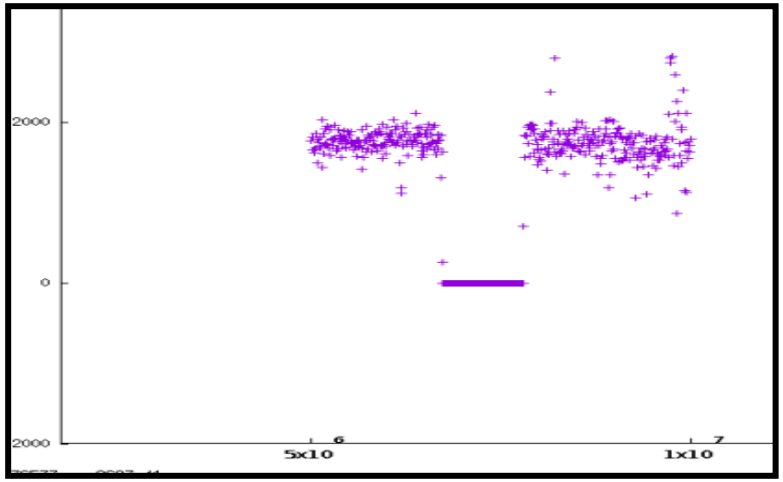

500kb deletion, Sahana et al, (under preparation)

# Check for deletions

## Other detected haplotypes

- Not large deletion
- Could be small deletion, point mutation
- False positive




Position

# Future work plan

- **Phenotype: reproductive trait**

  Insemination outcome from carrier-sire by carrier-dam mating vs. other matings

- **Application: Following the carrier frequencies**
  - limited use of high-merit carriers as bull sires
  - Add the 'diagnostic' markers in LD-chip

# Acknowledgement

- **Nordic Cattle Genetic Evaluation**
- **VikingGenetics**

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# Thank you for your attention!